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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/162,648	09/29/1998	JOHN C. HISERODT		9087

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EXAMINER	
CHEN, SHIN LIN	
ART UNIT	PAPER NUMBER
1632	21

DATE MAILED: 04/03/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/162,648	Applicant(s) HISERODT, JOHN C.	
	Examiner Shin-Lin Chen	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18,21 and 22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18,21 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's amendment filed 1-18-02 has been entered. Claims 21 and 22 have been added. Claims 1-22 are pending and under consideration.

Claim Rejections - 35 USC § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1-10, 12-16 and 18-20 remain rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Granger (US Patent 5,837,233) and is repeated for the reasons of record. Applicant's arguments filed 1-18-02 have been fully considered but they are not persuasive.

Applicant argues that in view of the context of the Granger patent and the claims in the patent, the cited phrase "In accordance with conventional prudent formulating practices, a

dosage..." in previous Official action does not mean the sequential administrations of MLC cells should be made to the same patient and it is not reasonable to open up a patient's skull on a daily or weekly basis (amendment, page 3). This is not found persuasive because the Granger patent only teaches treating glioblastoma (brain tumor) in example 1, it teaches treating melanoma and pancreatic cancer in example 2 and 3, respectively. The patent also describes treating other cancers, such as lung tumors, colon tumors, breast tumors, and prostate cancers. When a physician treats a patient having tumors other than brain tumors, he needs not open up patient's skull for treatment. Therefore, the phrase "In accordance with conventional prudent formulating practices, a dosage..." cited in previous Official action can be interpreted as having multiple doses of alloactivated lymphocytes administered to the **same** patient for treating tumors other than brain tumor.

Applicant argues that Granger only teaches one dose in examples 2 and 3 in treating melanoma and pancreatic cancer, respectively, and the reader must interpret the passage in light of what is taught in the rest of the patent disclosure (amendment, page 4). This is not found persuasive because of reasons of record and the reasons set forth above. Absence of teaching multiple doses in examples 2 and 3 does not necessarily mean that multiple doses of alloactivated lymphocytes is not allowed for treating tumors other than brain tumor.

Applicant cites Figure 2 of Granger patent and argues that only 2 of the 9 patient surviving beyond the period of study yet no second dose was given to the patient to generate more vigorous response (amendment, page 5). This is not found persuasive because of reasons

of record and the reasons set forth above. The data shown in Figure 2 is the data in treating brain tumor. As pointed out by the applicant in the argument, it is not reasonable to open up a patient's skull on a daily or weekly basis. Therefore, although the clinical data provided in the study in treating brain tumor (glioblastoma) does not show promising result, the patients were not given second dose because it is not reasonable to open up a patient's skull on a daily or weekly basis. Absence of using multiple doses in treating brain tumor does not necessarily mean that one can not use multiple dose in treating tumors other than brain tumor.

Applicant argues that claims 2-4 and 14 require using second dose even the first dose stimulates immune response, Granger does not teach or suggest using lymphocytes from third party donor, and the second dose is administered before the clinician assess the effect of first dose (amendment, page 6). This is not found persuasive because of reasons of record and the reasons set forth above. Granger teaches using lymphocytes from a human donor who is allogeneic to the patient and therefore, encompasses using the lymphocytes from third party donor. In addition to the teachings of Granger, it was known in the art that administration of multiple doses of an agent may improve clinical result in treating a disease. Thus, it would have been obvious for one of ordinary skill at the time of the invention to use second dose of alloactivated lymphocyte even before being able to assess the effect of the first dose.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (f) he did not himself invent the subject matter sought to be patented.

5. Claims 1-8, 12-14 and 18-20 remain rejected and claims 21 and 22 are rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter and is repeated for the reasons of record. Applicant's arguments filed 1-18-02 have been fully considered but they are not persuasive.

Claims 21 and 22 are newly added claims and are directed to the method of claim 1, wherein the tumor is not removed from the site at the time of implanting the first alloactivated cell population and the second cell population is implanted into the same tumor site as the first cell population, respectively.

Applicants argue that the first and second cell populations are both implanted into tumor bed and two implant procedures are required (amendment, page 7). This is not found persuasive because the PCT publication WO 98/16238 teaches implanting alloactivated cells after the tumor is resected and forms a cavity circumscribed by the **tumor bed** (e.g. p. 29, lines 14-16), and administration of alloactivated allogeneic lymphocytes into a solid tumor in the human or at or around a site where a solid tumor or a portion thereof has been removed (e.g. p. 58, lines 33-35). In fact, the added claims 21 and 22 read on implanting both cell populations when the tumor has

not been removed, which is taught by PCT publication WO 98/16238 as discussed above. Further, PCT publication WO 98/16238 teaches that additional doses may be given, such as on a monthly or weekly basis, until the desired effect is achieved (e.g. page 27, lines 39-40), and " in one preferred combination therapy, the subject is given an intra-tumor implant of stimulated allogeneic lymphocytes, either before, during, or after treatment at a site distant from the tumor with a composition comprising stimulated allogeneic lymphocytes and autologous tumor cells...Where a plurality of different compositions or modes of administration are employed...the order and timing of each element of treatment is chosen to optimize the immunostimulatory or anti-tumor effect" (e.g. p. 27, lines 19-29). Thus, PCT publication WO 98/16238 also teaches two implant procedures and claims 1-8, 12-14 and 18-20 remain rejected and claims 21 and 22 are rejected under 35 U.S.C. 102(f).

6. Claims 1-8, 12-14 and 18-22 are rejected under 35 U.S.C. 102(a) as being anticipated by Hiserodt et al., 1998, WO 98/16238.

Claims 1-8, 12-14 and 18-20 are directed to a method for treating cancer, such as melanoma, pancreatic cancer, liver cancer, colon cancer, prostate cancer, and breast cancer, in a human patient comprising implanting at or around the site of a tumor in the patient a first and a second cell populations containing alloactivated lymphocytes that are allogeneic to leukocytes in the patient, and the administration of the first and second cell populations is at an interval of at least three days, about one and eight weeks, or about two and twelve months, a method for

eliciting an anti-cancer immune response in a human patient by implanting the alloactivated lymphocytes set forth above, an a pharmaceutical composition comprising said alloactivated lymphocytes. Claims 21 and 22 are directed to the method of claim 1, wherein the tumor is not removed from the site at the time of implanting the first alloactivated cell population and the second cell population is implanted into the same tumor site as the first cell population, respectively.

Hiserodt teaches a method for stimulating an anti-tumor immunological response or treating a neoplastic disease, such as melanoma, pancreatic cancer, liver cancer, colon cancer, prostate cancer, and breast cancer, in a human comprising mixing *ex vivo* a first cell population comprising tumor cells, and a second cell population comprising lymphocytes allogeneic to the lymphocytes, to produce a cell mixture, and administering an effective amount of the cell mixture to the human (e.g. page 58-59). Hiserodt teaches alloactivated allogeneic lymphocytes can be administered into a solid tumor in the human or at or around a site where a solid tumor or a portion thereby has been removed (e.g. p. 58). Hiserodt also teaches that additional doses may be given, such as on a monthly or weekly basis, until the desired effect is achieved (e.g. page 27). Thus, claims 1-8, 12-14 and 18-22 are anticipated by Hiserodt.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 11 and 17 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Granger (US Patent 5,837,233) as applied to claims 1-10, 12-16 and 18-20 above, and further in view of Feldhaus et al. (US Patent 5,759,805) and Haugland (1992) and is repeated for the reasons of record. Applicant's arguments filed 1-18-02 have been fully considered but they are not persuasive.

Applicant argues the Granger does not teach or suggest administration of multiple dose to a single patient and both Feldhaus and Haugland do not teach harvesting alloactivated lymphocytes from culture at about the time of initial alloactivation (amendment, bridging page 7-8). This is not found persuasive because of reasons of record and the reasons set forth above. Jung teaches that CD69 is an antigen on human lymphocytes expressed during the early stage of cell activation. It would have been obvious for one of ordinary skill to harvest activated lymphocytes at about the time of initial alloactivation in order to measure cell activation by CD69 assay.

9. Claims 1, 2 and 6-8 remain rejected and claims 21 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kruse et al., 1994 (IDS-Ref. 18, Journal of Neuro-Oncology, 19: 161-168) and is repeated for the reasons of record. Applicant's arguments filed 1-18-02 have been fully considered but they are not persuasive.

Claims 21 and 22 are newly added claims and are directed to the method of claim 1, wherein the tumor is not removed from the site at the time of implanting the first alloactivated cell population and the second cell population is implanted into the same tumor site as the first cell population, respectively.

Applicant argues that CTL cited in Kruse reference has direct cytotoxic activity against the tumor which is different from a stimulator inducing a response by the host (amendment, page 8). This is not found persuasive because although direct killing of tumor cells by CTL is different from stimulating an immune response from a host having the tumor, the claims only recites stimulates **a response** in the patient but fails to specify what type of response is stimulated. A response could be any type of response from the host. The killing of tumors cells by CTL in a host could be considered a response from the host. Thus, claims 1, 2, 6-8, 21 and 22 are obvious for one of ordinary skill at the time of the invention according to the teachings of Kruse.

Applicant cites patents 5,837,233 and 6,136,306 and argues that there are four limitations that distinguish the Granger patents from the technology of Kruse and limitations 1 involves claim 1. Limitations 2-4 are irrelevant to the currently rejected claims. Limitation 1 is cited as "The implant cells have the ability to stimulate a response by the host against the tumor" (amendment, page 9). This is not found persuasive because of reasons of record and the reasons set forth above. The claim language in patents '233 and '306 is more specific than just "stimulate a response in a host" of the present application. Patent '233 specifies the implanted

cells **generate a therapeutic response against tumor growth** (see claims 1 and 17), and patent '306 specifies the **secretion of gamma interferon** by the alloactivated cells for implant (see claims 15, 17 and 20). The scope of claim 1 of the present application is much broader than the claims in patents '233 and '306. Claims 1, 2, 6-8, 21 and 22 are obvious for one of ordinary skill at the time of the invention according to the teachings of Kruse. Thus, claims 1, 2 and 6-8 remain rejected and claims 21 and 22 are rejected under 35 U.S.C. 103(a).

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Scott Priebe can be reached on (703) 308-7310. The fax phone number for this group is (703) 308-4242.

Questions of formal matters can be directed to the patent analyst, Patsy Zimmerman, whose telephone number is (703) 305-2758.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER